REMARKS

Claims 1-29 are currently pending in the application. Claims 1-5 and 7 have been amended and claims 6 and 8-29 have been withdrawn from further consideration.

Claims 1-5 have been amended to specify an "isolated" α-keto acid reductase. Claim 1 has been further amended to remove the term "produce" and to specify that the α-keto acid reduces 2-chlorophenyl glyoxylic acid (R)-2-chloromandelic acid and dehydrogenates the two optical isomers of 2-chloromandelic acid by no more than 20% compared to the dehydrogenation of 2-chlorophenyl glyoxylic acid, and that the α-keto acid reductase is encoded by (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1, (b) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2, or (c) a polynucleotide encoding an amino acid sequence comprising an amino acid sequence at least 95% homologous to the amino acid sequence of SEQ ID NO:2. Support for the amendments to claim 1 can be found, for example, at least at page 10, lines 2-6 and at page 11, lines 12-21 of the specification as originally filed.

Claim 7 has been amended to specify an "isolated" protein and to be in independent form. Support for the amendments to claim 7 can be found, for example, at least in original claim 6, and at page 5, lines 2-7 of the specification as originally filed.

The foregoing claim amendments should in no way be construed as acquiescence to any of the Examiner's rejections, and have been made solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed or as previously pending, in this or in one or more separate applications. No new matter has been added.

Objections to the Claims

Claim 7 is objected to as depending from a non-elected claim. Applicants have amended claim 7 to be in independent form. Therefore, this objection is moot.

Rejection of Claims 1-5 and 7 Under 35 U.S.C. §101

Claims 1-5 and 7 are rejected as being drawn to nonstatutory subject matter. In response, these claims have been amended, as suggested by the Examiner, to specify an "isolated" α-keto acid reductase or protein. Accordingly, this rejection is moot.

Rejection of Claims 1-5 and 7 Under 35 U.S.C. §112, Second Paragraph

Claims 1-5 and 7 have been rejected as being indefinite. Specifically, the Examiner requests clarification of the term "produce" and asserts that the phrase "substantially failing to dehydrogenate" is not clear.

With respect to the term "produce," Applicants have amended claim 1 to delete the term, as suggested by the Examiner. Accordingly, this rejection is moot.

With respect to the phrase "substantially failing to dehydrogenate," the Examiner asserts that "it is not clear...what is considered as 'substantially failing'."

Applicants respectfully traverse. Claim 1 specifies that the α-keto acid reductase "substantially fails to dehydrogenate either of the two optical isomers of 2-chloromandelic acid." The claimed functional property is clearly defined in the present specification, for example, at least at page 10, lines 2-6 of the specification as originally filed. Specifically, the specification states that

> "[s]ubstantially fails to dehydrogenate either of the two optical isomers of 2-chloromandelic acid" indicates that the dehydrogenase activity of an enzyme against either of the two optical isomers of 2-chloromandelic acid is 20% or lower taking the relative activity of the enzyme to reduce 2-chlorophenyl glyoxylic acid as 100%.

In addition, Applicants further teach (*e.g.*, at page 10, lines 7-24, and in Example 15 at pages 39-40) procedures and data for determining the substrate specificity of the α-keto reductase. In particular, Table 8 (page 40) provides data regarding a number of substrates that were incubated with the α-keto reductase obtained by the procedures outlined in Example 9, including (*R*,*S*)-2-chloromandelic acid and (*R*)-2-chloromandelic acid. The data shows that the

relative activity of the enzyme to reduce (*R*,*S*)-2-chloromandelic acid and (*R*)-2-chloromandelic acid was very low in comparison to the other α-keto acids listed in Table 8.

Notwithstanding the foregoing to expedite prosecution, claim 1 has been amended to specify that the isolated α-keto reductase reduces 2-chlorophenyl glyoxylic acid and dehydrogenates the two optical isomers of 2-chloromandelic acid by no more than 20% as compared to the dehydrogenation of 2-chlorophenyl glyoxylic acid. Accordingly, Applicants respectfully request the Examiner reconsider and withdraw this rejection.

Rejection of Claims 1-5 and 7 Under 35 U.S.C. §112, First Paragraph

Claims 1-5 and 7 are rejected as not meeting the written description requirement. Specifically, the Examiner asserts that

> the claims are drawn to a genus of polypeptides having any structure. The specification only teaches one species, the polypeptide of SEQ ID NO:2, isolated from *Leuconstoc mesenteroides* subsp. *dextranicum*, having α-keto acid reductase activity. This one species is not enough and does not constitute a representative number of species to describe the whole genus of any variants, recombinants and mutants of any α-keto reductase isolated from any source and "produced" in *Leuconostoc*, *Leuconostoc mesenteroides* or *Leuconstoc mesenteroides* subsp. *dextranicum* or any variants, recombinants and mutants of SEQ ID NO:2...Therefore, the specification fails to describe a representative species of the genus comprising any or all variants and mutants of SEQ ID NO:2 or any α-keto acid reductase isolated from any source...

The Examiner further asserts that "[c]laim 7 is also drawn to many functionally unrelated polypeptides encompassed within the scope of the claim..." and that

> [t]he specification fails to describe additional representative species of the polypeptides by any identifying characteristics or properties of the polypeptides, for which no predictability of function is apparent.

Applicants respectfully traverse. However, to expedite prosecution, claim 1 has been amended to define the isolated α-keto acid reductase by specific structural and functional features, *e.g.*, encoded by (a) a polynucleotide comprising the nucleotide sequence set forth in SEQ ID NO:1 (b) a polynucleotide encoding a protein comprising the amino acid sequence set

forth in SEQ ID NO:2 or (c) a polynucleotide encoding an amino acid sequence comprising an amino acid sequence at least 95% homologous to the amino acid sequence of SEQ ID NO:2.

Similarly, as amended, the isolated protein of claim 7 is also defined by specific structural and functional features, *e.g.*, encoded by a polynucleotide comprising the nucleotide sequence set forth in SEQ ID NO:1 or a polynucleotide encoding a protein comprising the amino acid sequence set forth in SEQ ID NO:2.

Moreover, with respect to the α-keto acid reductase encoded by a polynucleotide encoding an amino acid sequence which is at least 95% homologous to the amino acid sequence of SEQ ID NO:2, Applicants respectfully direct the Examiner's attention to Example 14 of the *Revised Interim Written Description Guidelines Training Materials* (published January 5, 2001; http://www.uspto.gov/web/menu/written.pdf), which provides that a claim directed to variants of a protein that are at least 95% identical to a particularly disclosed sequence and that have a particularly specified activity in combination with an accompanying specification that discloses a single species falling with the claimed genus, satisfies the requirements of 25 U.S.C. §112, first paragraph, for written description. Therein, the Office concludes that "the genus of proteins that must be variants . . . does not have substantial variation since all the variants must possess the specific catalytic activity and must have at least 95% identity to the reference sequence." The rationale behind the foregoing conclusion, as presented by the *Written Description Guidelines*, is that "[t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which Applicant provides for identifying all of the at least 95% identical variants...which are capable of the specified catalytic activity." Accordingly, one skilled in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus (*i.e.*, the sample claim meets the written description requirement of 35 U.S.C. §112, first paragraph). See, Training Materials, pages 53-55.

The subject matter as defined in claim 1 is analogous to the claim of Example 14 in the Guidelines in that the claims of the instant application are directed to a protein having at least 95% identity to a reference sequence, namely SEQ ID NO:2, and having a specifically identified activity, namely the reduction of α-keto acids to (*R*)-α-hydroxy acids. As discussed above,

since the species disclosed is representative of the claimed genus based, for example, on the defined structural and functional features, the claimed genus will not have substantial variation. Thus, it follows that since the genus is not widely variable, a single species (namely, SEQ ID NO:2) is sufficient to demonstrate possession.

Furthermore, the instant specification sets forth assays for identifying all of the at least 95% identical variants of SEQ ID NO:2 which perform the reduction of α-keto acids to (*R*)-α-hydroxy acids. Assays for determining α-keto acid reductase activity are set forth in the specification as originally filed, for example, at least at page 30, line 7 to page 34, line 3, at page 35, line 3 to page, 36, line 20, and at page 39, line 20 to page 40, line 4. Methods for introducing mutations and determining the percent sequence identity are also set forth in the specification as originally filed (for example, at page 13, line 5 to page 14, line 20).

Based at least on the foregoing, the present specification sufficiently describes the genus encompassed by claim 1 so as to convey with reasonable clarity to those skilled in the art that Applicants were in possession of the claimed invention.

Rejection of Claims 1-5 and 7 Under 35 U.S.C. §112, First Paragraph

Claims 1-5 and 7 are rejected as not being enabled. The Examiner is of the position that

> the specification, while being enabling for the polypeptide of SEQ ID NO:2 having α-keto acid reductase activity and all the properties recited in the claims, does not reasonably provide enablement for any or all mutants and variants of any α-keto reductase isolated from any source and "produced" in *Leuconostoc*, *Leuconostoc mesenteroides* or *Leuconstoc mesenteroides* subsp. *dextranicum*...

The Examiner further asserts that

> [c]laim 7 also broadly encompasses variants, mutants and recombinants having α-keto reductase activity, [and] polypeptides having any function or having no function. Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

Applicants respectfully traverse. However, as described above, to expedite prosecution independent claims 1 and 7 have been amended to define claimed molecules by specific structural and functional features.

Based at least on the foregoing, Applicants submit that claims 1-5 and 7 are fully enabled and respectfully request reconsideration and withdrawal of this rejection.

Rejection of Claims 1-5 and 7 Under 35 U.S.C. §102(b)

Claims 1-5 and 7 are rejected under 35 U.S.C. §102(b) as being anticipated by Leuchtenberger *et al.* In particular, the Examiner asserts that the '623 patent

> discloses an enzyme isolated from *Leuconostoc dextranicum*, where the enzyme reduces α-keto acids to (R)-α-hydroxyl acid using NAD+... *Leuconostoc dextranicum* is a synonym for *Leuconstoc mesenteroides* subsp. *dextranicum*...The enzyme of Leuchtenberger *et al.* inherently possesses the same material structure and functional characteristics of the enzyme of claims 1-2 since both enzymes are isolated from *Leuconstoc mesenteroides* subsp. *dextranicum* and have α-keto acid reductase activity.

Applicants respectfully traverse. As described above, independent claims 1 and 7 have been amended to define the claimed molecules by specific structural and functional features.

Applicants respectfully submit that Leuchtenberger *et al.* fail to teach or suggest the α-keto reductase of claim 1, where the α-keto reductase reduces 2-chlorophenyl glyoxylic acid ***and dehydrogenates the two optical isomers of 2-chloromandelic acid by no more than 20% compared to the dehydrogenation of 2-chlorophenyl glyoxylic acid.*** On the contrary, Leuchtenberger *et al.* describe (for example, at column 1, lines 44-56) the enzyme D-2-hydroxy-4-methylpentanoic acid dehydrogenase which is characterized by ***both the dehydrogenation*** of D-2-hydroxycarboxylic acids to the corresponding 2-ketocarboxylic acids ***and the reduction*** of 2-ketocarboxylic acids to the corresponding D-2-hydroxycarboxylic acids.

Further, Leuchtenberger *et al.* fail to teach or suggest the α-keto reductase of claim 1, where the α-keto acid reductase is encoded by (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1, (b) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2 or (b) a polynucleotide encoding an amino acid sequence comprising an amino acid sequence at least 95% homologous to the amino acid sequence of SEQ ID NO:2.

Moreover, Leuchtenberger *et al.* fail to teach or suggest an isolated protein, as claimed in claim 7, in which the protein is an enzyme that catalyzes the reduction of α-keto acids and is

encoded by a polynucleotide comprising the nucleotide sequence as set forth in SEQ ID NO:1 or a polynucleotide encoding a protein comprising the amino acid sequence as set forth in SEQ ID NO:2.

Finally, Applicants respectfully submit that the enzyme disclosed by Leuchtenberger *et al.* is a D-α-hydroxyisocaproic acid dehydrogenase (D-HicDH) (see page 4, lines 1-9 of the present specification) which has different properties compared to the claimed enzyme since α-hydroxyisocaproic acid is the same compound as 2-hydroxy-4-methylpentanoic acid. Specifically, Applicants state that

> ...known enzymes having the activity to NADH-dependently reduce α-keto acids include...D-α-hydroxyisocaproic acid dehydrogenase (D-HicDH)...highly purified from lactic acid bacteria etc., and various properties thereof have been clarified (Enzyme Microb. Technol., 14, 28-35 (1992); Appl. Environ. Microbiol., 68, 2, 947-951 (2002)). However, all of these dehydrogenases show a dehydrogenating activity on α-hydroxy acids corresponding to the α-keto acids. Hence, it appears that these known enzymes have different properties as compared to the α-keto acid reductase of the present invention.

Based at least on the foregoing, Leuchtenberger *et al.* fail to teach or suggest the α-keto reductase of claim 1 or the isolated protein of claim 7. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw this rejection of the claims.

SUMMARY

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. If there are any remaining issues or the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Applicants believe no additional fees are due with this response. However, if additional fees are due, please charge our Deposit Account No. 12-0080, under Order No. SHZ-015 from which the undersigned is authorized to draw.

Dated: May 24, 2006

Respectfully submitted,

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